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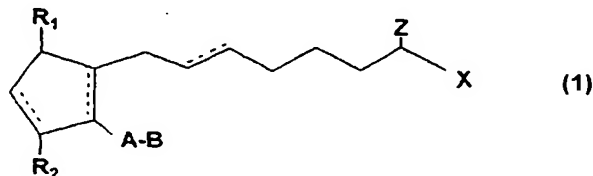
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10/345,788 15 January 2003 (15.01.2003) US(71) Applicant: **ALLERGAN, INC.** [US/US]; 2525 Dupont Drive, Irvine, CA 92612 (US).(72) Inventors: **WOODWARD, David, F.**; 22736 Islamare Lane, Lake Forest, CA 92630 (US). **VAN DENBURGH, Amanda, M.**; 8221 Mary Circle, Huntington Beach, CA 92646-5508 (US).(74) Agents: **BARAN, Robert, J.** et al.; c/o Allergan, Inc., 2525 Dupont Drive, Irvine, CA 92612 (US).(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).**Published:**

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- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **METHOD OF ENHANCING HAIR GROWTH**

(57) Abstract: Methods and compositions for stimulating the growth of hair are disclosed wherein said compositions include a cyclopentane heptanoic, 2-cycloalkyl or arylalkyl compound represented by the formula (1) wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A, B, Z, X R₁ and R₂ as defined in the specification. Such compositions are used in treating the skin or scalp of a human or non-human animal. Bimatoprost is preferred for this treatment.

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which the hair bulb is located superficially in the dermis. As alopecia progresses, a transition takes place in the area of approaching baldness wherein the hairs themselves are changing from the terminal to the vellus type.

Another factor that contributes to the end result is a change in the cycle of hair growth. All hair, both human and animal, passes through a life cycle that includes three phases, namely, the anagen phase, the catagen phase and the telogen phase. The anagen phase is the period of active hair growth and, insofar as scalp hair is concerned, this generally lasts from 3-5 years. The catagen phase is a short transitional phase between the anagen and telogen phases which, in the case of scalp hair, lasts only 1-2 weeks. The final phase is the telogen phase which, for all practical purposes, can be denominated a "resting phase" where all growth ceases and the hair eventually is shed preparatory to the follicle commencing to grow a new one. Scalp hair in the telogen phase is also relatively short-lived, some 3-4 months elapsing before the hair is shed and a new one begins to grow.

Under normal hair growth conditions on the scalp, approximately 88% of the hairs are in the anagen phase, only 1% in catagen and the remainder in telogen. With the onset of male pattern baldness, a successively greater proportion of the hairs are in the telogen phase with correspondingly fewer in the active growth anagen phase.

Alopecia is associated with the severe diminution of hair follicles. A bald human subject will average only about 306 follicles per square centimeter, whereas, a non-bald human in the same age group will have an average of 460 follicles per square centimeter. This amounts to a one-third reduction in hair follicles which, when added to the increased proportion of vellus hair follicles and the increased number of hair follicles in the telogen phase, is both significant and noticeable. Approximately 50% of the hairs must be shed to produce visible thinning of scalp hair. It is thus a combination of these factors: transition of hairs from terminal to vellus, increased number of telogen hairs--some of which have been shed, and loss of hair follicles that produces "baldness".

While a good deal is known about the results of male pattern baldness, very little is known about its cause. The cause is generally believed to be genetic and

of intermediate status in that it is coarser than vellus but not as coarse as terminal hair. The hair is generally quite short with a length of 3 cm. being about maximum. Once the patient ceases taking the drug, the hair reverts to whatever is normal for the particular site after six months to a year has elapsed. An example of such a drug is diphenylhydantoin which is an anticonvulsant drug widely used to control epileptic seizures. Hypertrichosis is frequently observed in epileptic children some two or three months after starting the drug and first becomes noticeable on the extensor aspects of the limbs and later on the trunk and face. (The same pattern of hypertrichosis is sometimes caused by injury to the head.) As for the hair, it is often shed when the drug is discontinued but may, in some circumstances, remain.

Streptomycin is another drug that has been found to produce hypertrichosis, in much the same way as diphenylhydantoin, when administered to children suffering from tuberculous meningitis. About the same effects were observed and the onset and reversal of the hypertrichosis in relation to the period of treatment with the antibiotic leave little question but that it was the causative agent.

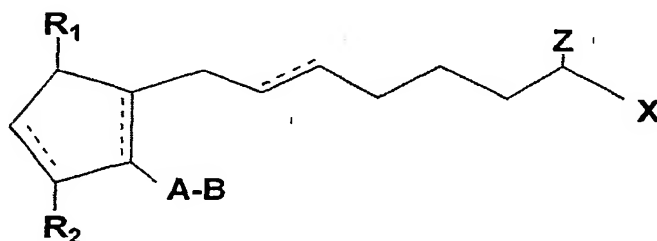
Two treatments have been demonstrated as showing some promise in reversing male pattern alopecia. These treatments include the use of a microemulsion cream containing both estradiol and oxandrolone as its active ingredients and the use of organic silicon.

In addition to the foregoing, it has been reported in U.S. Pat. Nos. 4,139,619 and 4,968,812 that the compound minoxidil is useful for the treatment of male pattern baldness. That compound, among others, has proven to have considerable therapeutic value in the treatment of severe hypertension. It is a so-called "vasodilator" which, as the name implies, functions to dilate the peripheral vascular system. Dermatologists and others have recognized that prolonged vasodilation of certain areas of the human body other than the scalp sometimes result in increased hair growth even in the absence of any vasodilating therapeutic agent. For instance, increased hair growth around surgical scars is not uncommon. Similarly, arteriovenous fistula have been known to result in increased vascularity

Other objects of the invention are to provide a treatment for male pattern alopecia which is safe, simple, painless, cosmetic in the sense of being invisible; easy to apply and quite inexpensive when compared with hair transplants and the like.

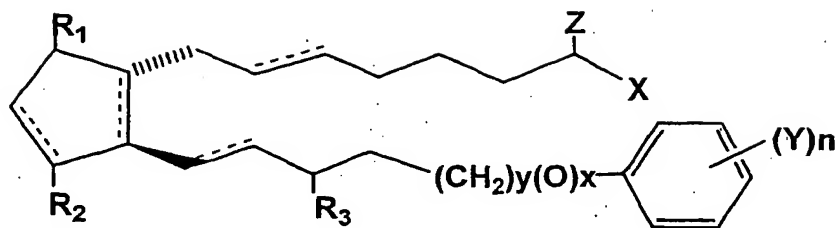
SUMMARY OF THE INVENTION

This invention provides pharmaceutical compositions for topical application to enhance hair growth comprising an effective amount of a cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compound represented by the formula I



wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxa radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is -N(R⁴)₂ wherein R⁴ is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,

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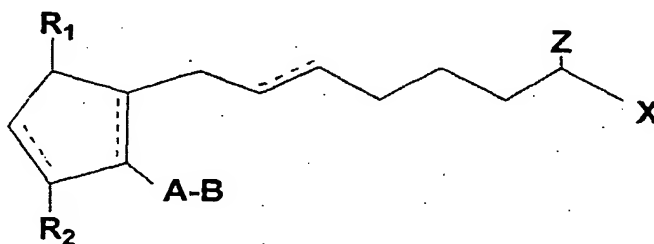


wherein hatched lines indicate α configuration, solid triangles are used to indicate β configuration.

More preferably y is 1 and x is 0 and R_1 , R_2 and R_3 are hydroxy.

Most preferably the compound is cyclopentane N-ethyl heptanamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1 α ,2 β ,3 α ,5 α], also known as bimatoprost.

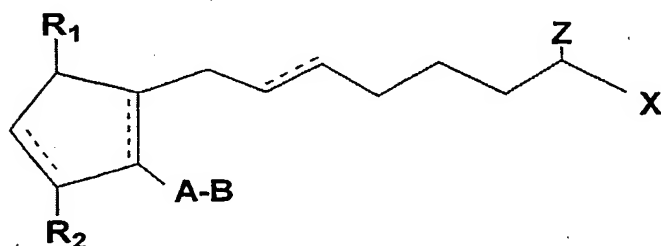
Another aspect of the invention provides methods for stimulating the rate of hair growth and for stimulating the conversion of vellus hair or intermediate hair to growth as terminal hair in a human or non-human animal by administering to the skin of the animal an effective amount of a compound wherein the compound has the formula:



wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxa radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical,

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examination to determine its presence. This vellus hair is a precursor to terminal hair. In accordance with the invention as described herein, compounds represented by



wherein R_1 , R_2 , A, B, Z and X are defined above, can be used to stimulate, such as stimulating the conversion of vellus hair to growth as terminal hair as well as increasing the rate of growth of terminal hair.

The present invention was discovered as follows:

In the course of treating patients having glaucoma, treatment may only be appropriate in one eye. Within the course of daily practice it was discovered that a patient who been treated with bimatoprost has lashes that were longer, thicker and fuller in the treated eye than in the non-treated eye. On examination the difference was found to be very striking. The lashes were longer and had a more full dense appearance in the treated eye. The lash appearance on the lids of the treated eye would have appeared quite attractive if it represented a bilateral phenomenon. Because of its asymmetric nature, the long lashes on one side could be construed as disturbing from a cosmetic standpoint. Because of the very unusual appearance a systematic examination of other patients who were taking bimatoprost in only one eye was made. It soon became apparent that this altered appearance was not an isolated finding. Comparison of the lids of patients who were taking bimatoprost in only one eye revealed subtle changes in the lashes and adjacent hairs of the bimatoprost-treated side in several patients. Definite differences could be identified to varying degrees in the lashes and adjacent hairs of all patients who were taking the drug on a unilateral basis for longer than 6 months.

than hair on, for example, the scalp. The ability to cause differences in appearance of lashes, the ability to stimulate conversion of vellus or intermediate hair to terminal hairs in transitional areas and the ability to stimulate growth of vellus hair on the skin indicates that bimatoprost is a diversely effective and efficacious agent for the stimulation of hair growth. Thus, the present invention provides a treatment by bimatoprost of hair of the scalp, eyebrows, beard and other areas that contain hair that results in increased hair growth in the corresponding areas.

Patients that are treated in or around the eye with compounds of the invention, such as bimatoprost, regularly develop hypertrichosis including altered differentiation, numbers, length, thickness, curvature and pigmentation in the region of treatment.

Some examples of representative compounds useful in the practice of the present invention include the compounds shown in Table 1:

TABLE 1

cyclopentane heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]

cyclopentane N,N-dimethylheptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]

cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-meta-chlorophenoxy-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]

cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-trifluoromethylphenoxy-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]

cyclopentane N-isopropyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]

growth includes hair associated with the scalp, eyebrows, eyelids, beard, and other areas of the skin of animals.

In accordance with one aspect of the invention, the compound is mixed with a dermatologically compatible vehicle or carrier. The vehicle which may be employed for preparing compositions of this invention may comprise, for example, aqueous solutions such as e.g., physiological salines, oil solutions or ointments. The vehicle furthermore may contain dermatologically compatible preservatives such as e.g., benzalkonium chloride, surfactants like e.g., polysorbate 80, liposomes or polymers, for example, methyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid; these may be used for increasing the viscosity. Furthermore, it is also possible to use soluble or insoluble drug inserts when the drug is to be administered.

The invention is also related to dermatological compositions for topical treatment for the stimulation of hair growth which comprise an effective hair growth stimulating amount of one or more compounds as defined above and a dermatologically compatible carrier. Effective amounts of the active compounds may be determined by one of ordinary skill in the art but will vary depending on the compound employed, frequency of application and desired result, and the compound will generally range from about 0.0000001 to about 50%, by weight, of the dermatological composition, preferably from about 0.001 to about 50%, by weight, of total dermatological composition, more preferably from about 0.1 to about 30%, by weight of the composition.

The present invention finds application in all mammalian species, including both humans and animals. In humans, the compounds of the subject invention can be applied for example, to the scalp, face, beard, head, pubic area, upper lip, eyebrows, and eyelids. In animals raised for their pelts, e.g., mink, the compounds can be applied over the entire surface of the body to improve the overall pelt for commercial reasons. The process can also be used for cosmetic reasons in animals, e.g., applied to the skin of dogs and cats having bald patches due to mange or other diseases causing a degree of alopecia.

for instance, based on substances forming in-situ gels. Depending on the actual formulation and compound to be used, various amounts of the drug and different dose regimens may be employed. Typically, the daily amount of compound for treatment of the eyelid may be about 0.1 ng to about 100 mg per eyelid.

For topical use on the skin and the scalp, the compound can be advantageously formulated using ointments, creams, liniments or patches as a carrier of the active ingredient. Also, these formulations may or may not contain preservatives, depending on the dispenser and nature of use. Such preservatives include those mentioned above, and methyl-, propyl-, or butyl-parahydroxybenzoic acid, betain, chlorhexidine, benzalkonium chloride, and the like. Various matrices for slow release delivery may also be used. Typically, the dose to be applied on the scalp is in the range of about 0.1 ng to about 100 mg per day, more preferably about 1 ng to about 10 mg per day, and most preferably about 10 ng to about 1 mg per day depending on the compound and the formulation. To achieve the daily amount of medication depending on the formulation, the compound may be administered once or several times daily with or without antioxidants.

The invention is further illustrated by the following non-limiting examples:

Example 1

In Vivo Treatment

A study is initiated to systematically evaluate the appearance of lashes and hair around the eyes of patients who are administering bimatoprost in only one eye. The study involves 10 subjects, 5 male, 5 female, average age 70 years, (ranging from 50-94 years). All patients have glaucoma. Each subject is treated daily by the topical application of one drop of bimatoprost at a dosage of 1.5 .mu.g/ml/eye/day (0.03%, by weight, ophthalmic solution, sold under the name Lumigan® by Allergan, Irvine, California, U.S.A.) to the region of one eye by instilling the drop onto the surface of the eye. The region of the fellow control eye is not treated with bimatoprost and served as a control.

actual lashes. These long, thick lash-like hairs were present in the central portion of the lids of several patients in a linear arrangement just above the lash line. Hairs are present at similar locations in the control eyes but are by contrast thinner or more fine in appearance, have less luster and pigment and are more flat against the skin of the lid typical of vellus or intermediate hairs. In several patients, lash-like terminal hairs grow luxuriantly in the medial canthal area in the treated eye. In the corresponding control eye, vellus hairs are seen at the same location. Lash-like hairs are also present in the lateral canthal area of the treated eye but not the control eye in several subjects. Large lashes are not normally present at the lateral canthus and the area is generally free of all but a few occasional very fine lashes or vellus hairs.

Increased growth of vellus hair on lids: Fine microscopic vellus hair is present on the skin of the lids and is easily seen with the slit lamp biomicroscope. This vellus hair is typically denser adjacent to and below the lateral portion of the lower lids. While remaining microscopic, vellus hairs are increased in number, appear more robust and are much longer and thicker in treated than in control eyes in the areas below and lateral to the lower lid.

Perpendicular angulation of hairs: In areas where there are lash-like hairs above the lash line and in the medial and lateral canthal areas, the hairs are much longer, thicker and heavier. They also leave the surface of the skin at a more acute angle, as though they are stiffer or held in a more erect position by more robust follicles. This greater incline, pitch, rise or perpendicular angulation from the skin surface gives the appearance of greater density of the hairs.

The foregoing observations clearly establish that bimatoprost can be used to increase the growth of hair in man. This conclusion is based on the regular and consistent finding of manifestations of increased hair growth in treated vs. control areas in human subjects. The conclusion that the drug bimatoprost is capable of inducing increased robust growth of hair is based not on a single parameter, i.e., length, but is based on multiple lines of evidence as described in the results.

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The composition is applied to bald human scalp once daily to stimulate the growth of hair.

Example 4

Topical Ointment

An ointment containing 2% by weight bimatoprost is prepared as follows:

White petrolatum and wool fat are melted, strained and liquid petrolatum is added thereto. The bimatoprost, zinc oxide, and calamine are added to the remaining liquid petrolatum and the mixture milled until the powders are finely divided and uniformly dispersed. The mixture is stirred into the white petrolatum, melted and cooled with stirring until the ointment congeals.

The foregoing ointment can be applied topically to mammalian skin for increased rate of hair growth, and can be prepared by omitting the zinc oxide and calamine.

Example 5

Ointment

A dermatological ophthalmic ointment containing 10% by weight bimatoprost is prepared by adding the active compound to light liquid petrolatum. White petrolatum is melted together with wool fat, strained, and the temperature adjusted to 45-50° C. The liquid petrolatum slurry is added and the ointment stirred until congealed. Suitably the ointment is packaged in 30 gm tubes.

The foregoing ointment can be applied to the eyelid to enhance the growth of eyelashes. Similarly the composition can be applied to the brow for eyebrow growth.

Example 9

Dusting Powder

A powder of the compound bimatoprost is prepared by mixing in dry form with talcum powder at a weight/weight ratio of 1:10. The powdered mixture is dusted on the fur of minks or other commercially valuable fur bearing animals and show animals for increased rate of hair growth.

Example 10

Related Compounds

Following the procedure of the preceding Examples, compositions are similarly prepared substituting an equimolar amount of a compound of Table 1 for the bimatoprost disclosed in the preceding Examples. Similar results are obtained.

While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

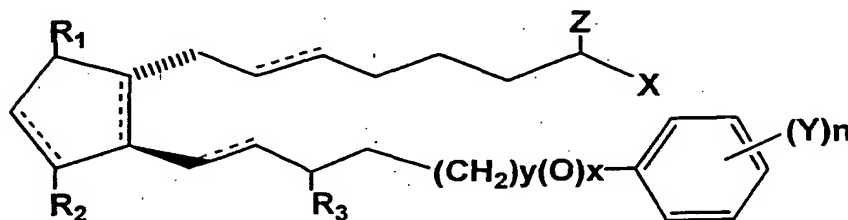
The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:



$\text{R}^5\text{-C-}$ and $\text{R}^5\text{-O-C-}$, wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is $=\text{O}$; one of R_1 and R_2 is $=\text{O}$, $-\text{OH}$ or a $-\text{O}(\text{CO})\text{R}_6$ group, and the other one is $-\text{OH}$ or $-\text{O}(\text{CO})\text{R}_6$; or R_1 is $=\text{O}$ and R_2 is H , wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $-(\text{CH}_2)_m\text{R}_7$ wherein m is 0 or an integer of from 1 to 10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above or a pharmacologically acceptable acid addition salt thereof.

2. The method of claim 1 wherein the concentration of the compound applied is from about 0.0000001% to about 50% by weight of the composition.

3. The method of claim 1 wherein the compound is a compound of formula (III).



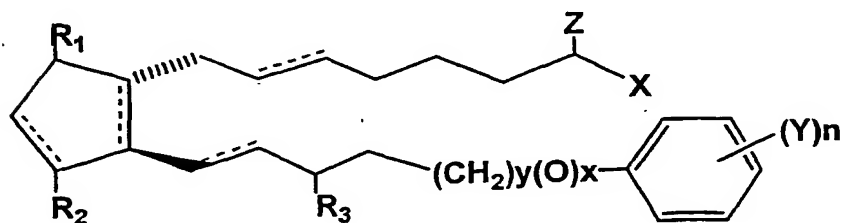
wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, n is 0 or an integer of from 1 to about 3 and R_3 is $=\text{O}$, $-\text{OH}$ or $-\text{O}(\text{CO})\text{R}_6$ wherein R_6 , hatched lines indicate α configuration and solid triangles are used to indicate β configuration.



$\text{R}^5\text{-C-}$ and $\text{R}^5\text{-O-C-}$, wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is $=\text{O}$; one of R_1 and R_2 is $=\text{O}$, $-\text{OH}$ or a $-\text{O}(\text{CO})\text{R}_6$ group, and the other one is $-\text{OH}$ or $-\text{O}(\text{CO})\text{R}_6$, or R_1 is $=\text{O}$ and R_2 is H , wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $-(\text{CH}_2)_m\text{R}_7$ wherein m is 0 or an integer of from 1 to 10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above or a pharmacologically acceptable acid addition salt thereof.

6. The method of claim 5 wherein the concentration of the compound applied is from about 0.0000001% to about 50% by weight of the composition.

7. The method of claim 5 wherein the compound is a compound of formula (III).



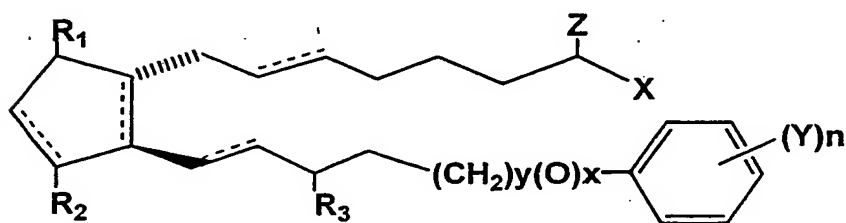
wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, n is 0 or an integer of from 1 to about 3 and R_3 is $=\text{O}$, $-\text{OH}$ or $-\text{O}(\text{CO})\text{R}_6$, hatched lines indicate α configuration and solid triangles are used to indicate β configuration.

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the other one is -OH or -O(CO)R₆, or R₁ is =O and R₂ is H, wherein R₆ is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or -(CH₂)_mR₇ wherein m is 0 or an integer of from 1 to 10, and R₇ is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above or a pharmacologically acceptable acid addition salt thereof.

10. The method of claim 1 wherein the concentration of the compound applied is from about 0.0000001% to about 50% by weight of the composition.

11. The method of claim 10 wherein the compound is a compound of formula (III).



wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, n is 0 or an integer of from 1 to about 3 and R₃ is =O, -OH or -O(CO)R₆ wherein R₆, hatched lines indicate α configuration and solid triangles are used to indicate β configuration.

12. The method of claim 11 wherein the compound is bimatoprost or a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US 03/03363

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | "Bimatoprost (Ophtalmic)" MEDLINEPLUS. HEALTH INFORMATION, 'Online! 24 July 2001 (2001-07-24), XP002245126 Retrieved from the Internet: <URL:www.nlm.nih.gov/medlineplus/druginfor/ /uspd/500295> 'retrieved on 2003-06-23! *see "Precautions while using this medicine" and "Side effects" | 1-12 |
| X | US 6 262 105 B1 (JOHNSTONE MURRAY A) 17 July 2001 (2001-07-17) column 7, line 55-65; claim 1; table 1 | 1-12 |
| A | US 5 607 978 A (BURK ROBERT M ET AL) 4 March 1997 (1997-03-04) cited in the application the whole document | 1-12 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

23 June 2003

Date of mailing of the international search report

10/07/2003

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